i. Review article: The aetiology of fatigue in Inflammatory Bowel Disease and potential therapeutic management strategies

ii. Aetiology and management of IBD Fatigue

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Vi. Structured summary

Background: Fatigue is the inability to achieve or maintain an expected work output resulting from central or peripheral mechanisms. The prevalence of inflammatory bowel disease (IBD) fatigue can reach 86% in active disease, persisting in 50%-52% of patients with mild to inactive disease. Fatigue is the commonest reason for work absence in IBD, and patients often report fatigue burden to be greater than that of primary disease symptoms. Relatively few evidence-based treatment options exist, and the aetiology is poorly understood.

Aim: To review the available data and suggest a possible aetiology of IBD fatigue and to consider the efficacy of existing management strategies and highlight potential future interventions.

Methods: We reviewed fatigue-related literature in IBD using PubMed database.

Results: Disease related factors such as inflammation and pharmacological treatments negatively impact skeletal muscle and brain physiology, likely contributing to fatigue symptoms. Secondary factors such as malnutrition, anaemia, sleep disturbance and psychological comorbidity are potential determinants. Immune profile, faecal microbiota composition and physical fitness differ significantly between fatigued and non-fatigued patients, suggesting these may be aetiological factors. Solution-focused therapy, high-dosage thiamine supplementation and biological therapy may reduce fatigue perception in IBD. The effect of physical activity interventions is inconclusive.

Conclusions: A multimodal approach is likely required to treat IBD fatigue. Established reversible factors like anaemia, micronutrient deficiencies and active disease should initially be resolved. Psychosocial intervention shows potential efficacy in reducing fatigue perception in quiescent disease. Restoring physical deconditioning by exercise training intervention may further improve fatigue burden.

Keywords: Inflammatory Bowel Disease, Tiredness, Weakness, Fatigue Perception, Skeletal muscle, Exercise-training, Metabolic deconditioning.

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vii. Main text

Introduction

Fatigue is a common secondary disease symptom in inflammatory bowel disease (IBD). Affected patients report heavy limbs[1] and impaired concentration[1] and demonstrate premature loss of muscle force during exercise.[2] Fatigue is associated with increased mortality[3]and impairs health-related quality of life.4 IBD patients report fatigue-related burden to be greater than classical symptoms such as bowel urgency and diarhoea,[5] illustrating the pervasiveness of the symptom. However, the symptom is rarely prioritised in clinicalconsultations[6] as it is poorly understood by both clinicians[7] and patients.[8] Fatigue is associated with absenteeism[9] and is the commonest reason for work absence in IBD (51%), exceeding that of medical appointments (49%) and abdominal pain (46%).[10] These factors likely contribute to the early retirement, reduced personal achievement and increased unemployment reported in IBD.[11] This is important as low socio-economic status is associated with increased hospitalisation and mortality in Crohn's disease[12] and limited employment status is associated with IBD fatigue (2.50, 1.16-5.39,P = 0.02).[13]The prevalence of fatigue complaints is as high as 86% in patients with active disease[14] and 50%-52%of patients with inactive or mild disease continue to report substantial fatigue compared to22% of healthy controls.[15] The persistence of fatigue during disease remission, independent of reversible clinical causes such as anaemia, malnutrition, hypothyroidism and B12 deficiency16 is consistent with other autoimmune disease.[17] Despite an extensive literature base on fatigue and the recent prioritisation of IBD fatigue research by the Nurses-European Crohn's and Colitis Organisation (N-ECCO)and the IBD priority setting partnership with the James Lind alliance,[18,19]fatigue aetiology remains poorly understood, which limits treatment options. Psychosocial[20] and pharmacological[14,21,22] treatments have shown potential efficacy in targeting IBD fatigue, although no conclusive data are available.

Aims

The primary aim of this review is to provide an overview of available IBD data to build a theoretical model for IBD fatigue aetiology. We review the efficacy of existing fatigue interventions and provide recommendations for future management strategies. We speculate on the potential role of muscle deconditioning in the aetiology of IBD fatigue and the potential for exercise training intervention to improve fatigue burden.

Fatigue Perception

Fatigue severity is quantified by self-reportedscales[23] designed to measure chronic fatigue burden over a proceeding period or acute fatigue responses to a task.[24] There are multiple domains of fatigueperception[25] linked to specific neural mechanisms. IBD patients have self-reported physical and cognitive fatigue[1] (i.e., the perception of reduced performance in physical and cognitive tasks), which is modulated by the contralateral sensorimotor cortex[26] and the frontoparietal network.[27] Motivational fatigue is another facet which may relate to altered orbitofrontal cortex activity, due to its role in decisionmaking.[28]Determining the clinical significance of perceived fatigue is problematic[29,30]and is usually ascertained when fatigue scores are significantly elevated relative to a healthy control group.[15] Stratifying IBD patients into perceived fatigued and non-fatigued subgroups using self-reported scales has revealed reduced cardiorespiratory fitness and muscle strength[31] and alterations in immune profile[32] and faecalmicrobiota[33] in fatigued patients relative to those without, highlighting a potential aetiological role of these factors. However, a variety of assessment scales have been used to assess perceived fatigue[34] and absence of consensus on the use of such scales impairs harmonisation

of data sets across multiple cohorts. A consensus approach on standardised measurement of perceived fatigue burden in IBD using validated scales would aid in better defining fatigue aetiology.

Exercise Fatigue

Sustained exercise is maintained via integration of central nervous system (CNS), cardiorespiratory and musculoskeletal systems.[35]Reductions in motor cortical, spinal motor neuron output and impaired neuromuscular junction transmission inhibit neural drive to skeletal muscle, leading to force loss,[35] termed supraspinal or centralfatigue.[36] Concomitantly, changes in ventilatory and cardiovascular responses during exercise can impede substrate supply and removal to and from contracting muscle. At an intramyocellular level, reliance on anaerobic ATP synthesis causes metabolite accumulation and/or substrate depletion[37,38] and eventual bioenergetic failure, termed peripheral fatigue.[39] These processes are typically accentuated in chronic disease.[40,41]Exercise fatigue can be quantified across a range of task modalities including repeated maximum isometric contractions and submaximal dynamic contractions.[42-44]Application of electrophysiological measurements during such tasks[45,46] can delineate contributions of my electrical failure to force loss.[36] However, these methods are limited in usefulness as they quantify fatigue duringlaboratory-basedexercise tasks and it is largely unknown how this relates to real world performance.[30]Relative to healthy controls, instantaneous maximal isometric knee extensor strength is less in IBD patients when normalised to fat free mass ($P < 0.001$)[47] and body mass ($P = 0.039$),[48] a s i sknee extensor endurance during both isometric ($P < 0.001$)[47]and maximal repeated isokinetic contractions ($P = 0.047$),[2] the latter of which correlates with fatigue perception ($r2 = −0.52, P < 0.01$).[2] Consistently, dynamic lower limb function assessed by a 12-repetitionsit up test was 25% slower

in Crohn's disease47 and32% slower in ulcerative colitis (UC) with mixed disease activity49relative to healthy controls. Similarly, gait speed was reduced by17% in IBD.[49] Handgrip strength in quiescent Crohn's disease patients is consistent with healthy controls when normalised to body cellmass[50] and fat-freem ass[47] but was less in a cohort o f 5 0 U C patients(P = 0.001).[50] This may relate to the reduced body cell mass in malnourished UC patients relative to well-nourished UC patients(P = 0.044),50 a s t his i s not observed i n Crohn's d isease.[50] Both groups had comparable rates of previous corticosteroid therapy, arguing against a treatment related effect. Handgrip *z* scores were reduced in some paediatric IBD cohorts with quiescent to mild disease activity (−0.34 vs 0.83, $P \leq 0.015$)[51]but maintained in others with mixed disease activity[52] relative to healthy children. Peripheral muscle strength ($P < 0.05$) and endurance($P < 0.01$) normalised to fat free mass is less in female Crohn's disease patients relative to males,[47] suggesting a gender effect in IBD fatigue.[49,53] This warrants further investigation as female gender is a risk factor for greater fatigue perception in IBD.[54]Cardiorespiratory fitness is also less in IBD relative to healthy controls. The blood lactate threshold assessed during preoperative incremental exercise testing, occurred at a lower VO2 in IBD patients compared to gender-specific reference values ($P <$ 0.0001),[55]and heart rate recovery was longer relative to healthy controls following an exercise stress test ($P < 0.001$).[56] Moderate-to-large effect sizes have been reported for reduced cardiorespiratory fitness ,muscle function and physical activity in fatigued IBD patients, relative to those without fatigue complaints and healthy controls.[31] Some data suggest exercise performance may decline as a functionof disease activity. Following protocolectomy and resection in Crohn's disease patients,57 peak aerobic workload achieved during incremental exercise testing was reduced relative to reference subjects in the no resection group (<10 cm ileal resection) in female Crohn's disease only ($P < 0.05$),[57] whereas peak workload

was reduced in all patients with moderate small bowel resection (15%-30%,$P < 0.01$). This was consistent in patients with >50% small bowel resection ($P < 0.01$), w here peak workload was also lower than the non-resected patient group ($P < 0.05$).

Factors associated with IBD Fatigue

Given the absence of data pertaining to fatigue aetiology in IBD,factors relating to disease pathophysiology and associated changes across organs which are known to associate with fatigue can help to establish possible origins (Figure 1).

Sleep disturbance

Sleep difficulties are associated with an increased risk of fatiguedevelopment[58] and with multiple facets of fatigue perception i n IBD.[13] Poor sleep quality is reported in 82% of Crohn's disease and in 72% of UC in active disease. In quiescent disease, 51% of Crohn's disease and 47% UC report sleep difficulties.[59] Classical disease symptoms are likely to affect sleep pattern. Factors such as faecal incontinence, abdominal pain and urgency as well as concerns over potential stoma leakages, which are commoner in patients with more active disease states, are likely to disturb sleep pattern and directly contribute to acute fatigue symptoms such as daytime sleepiness, which is associated with IBD fatigue.[60] Consistently, reduced sleep quality is also associated with multiple facets of fatigue perception in IBD.[13]The relationship between sleep disturbance, inflammation and disease activity in IBD is inherently difficult to characterise experimentally and may be bidirectional in nature. In healthy volunteers, acute interleukin-6(IL-6)administration reduces sleep quality and increases fatigue symptoms,[61] whilst sleep restriction elevates plasma tumour necrosis

factor alpha (TNF)[62] and IL-6[63]concentrations.Inactive IBD patients with disturbed sleep have a greater rate of 6-monthrelapse relative to patients without sleep difficulties.[64]Thus, it has been postulated that active disease and associated inflammatory burden may worsen sleep quality, and increase fatigueburden,[65] although other mechanisms may predominate when sleep disturbance persists when in clinical remission.[59]

Inflammation

Fatigue is prevalent in inflammatory disease[66] and active disease predicts fatigue burden in these diseases. Cytokine-based hypotheses for fatigue have been proposed, mediated by a link between the immune system and CNS.[67-69]Of relevance in IBD is the gut–brain axis, where vagal sensory neurons express receptors capable of sampling inflammatory mediators.[70] Pro-inflammatory cytokines can also act peripherally.[71,72] TNF inhibits skeletal muscle contractile function[73,74] via TNFR1-dependentmechanisms[71] and metabolically through impaired insulin-mediated glucose disposal, via AKTS160inhibtion.[72] TNF inversely correlated with lean body mass ($r2 = 0.33$,$P = 0.023$) in active Crohn's disease with increased serum TNF levels relative to controls ($P < 0.01$).[75] In quiescent IBD, an increased plasma IL-6concentration was independently associated with greater rate of knee extensor fatigue (2.84 [1, 8.08], $P = 0.05$).[2]Whether this is an indirect or direct association is unknown, but data from this laboratory showing a trend for increased plasma TNF concentrations in anabolically resistance paediatric Crohn's disease with mixed disease activity ($P = 0.078$) and reduced appendicular muscle mass index compared to age-matched controls ($P = 0.052$),[52] suggests it is indirect and mediated by inflammation induced reductions in muscle mass and quality. Inflammation may be an aetiological factor in active disease,[76] where fatigue prevelance[16] and severity[77] are greater relative to inactive disease. However, targeting disease activity6fails to improve fatigue burden in

most patients.[14,78] To this effect, fatigue complaints and performance deficits persist even in well-controlled disease, shown by a reduced plasma TNF-alpha(P = 0.002) and increased IL-10(P = 0.01)[2] compared to controls. Similarly, plasma concentrations of IL-12,IL-8and IL-5were no different between fatigued and non-fatigued patients with quiescent disease defined by Harvey Bradshaw Index (HBI) and modified Mayo score.[79] Further data s how consistent serum I L-6 concentrations between fatigued and non-fatigued IBD patients in endoscopicremission.[33] However, increased serum levels of IL-12,IL-10and stimulated TNF and IFN-y were reported in quiescent patients with fatigue relative to non-fatigued patients. Remission was defined as faecal calprotectin of <200 mg/g in the fatigued cohort and HBI <5 Crohn's disease and CAI <10 UC in the non-fatigued group (Figure 2).[32]Inflammation is clearly a contributor to active disease fatigue[15];however, current data do not support the role of subclinical inflammation in quiescent disease fatigue. Available data on inflammatory markers in quiescent disease fatigue are inconsistent and are likely confounded by varying definitions of disease remission and fatigue status.

Fatigue and the nutritional spectrum

Malnutrition and obesity

Up to 75% of hospitalised Crohn's disease patients are malnourished, and 50% are in negative nitrogen balance.[80] Inflammation is linked to anorexia, [81] whilst classic symptoms including abdominal pain, vomiting and diarrhoea[82] further contribute to general feeling of malaise and loss of appetite. Other factors such as altered eating behaviour due to hospitalisation and self-imposed dietary restrictions implemented to control GI symptoms[83,84] further impede dietaryintake[85,86] and contribute to malnutrition.IBD patients present with a number of micronutrient deficiencies

linked to fatigue[50] such as iron, vitamin D ,[87,88] vitamin B12[89]and thiamine.[90]Anaemia is reported in 27% of Crohn's disease and 21% of UC patients with an overall prevalence in IBD of 24%.[91] The aetiology is multifactorial, commonly occurring due to blood losses and reduced iron absorption.[92] The prevalence of iron deficiency anaemia is reported at 20% in IBD,[93] whilst iron deficiency in the absence of anaemia is reported at 37%.[94] Iron supplementation is associated with reduced fatigue burden in healthy subjects with non-anaemic iron deficiency but has no effect on objective performance.[95] Fatigue perception does not differ in IBD patients with and without iron deficiency, suggesting no association between iron deficiency and perceived fatigue when assessed independently of anaemia.[96]In a cohort of 140 IBD patients, haemoglobin concentrations were weakly correlated to chronic fatigue perception in 20 UC patients with quiescent to mild or moderate disease ($\beta = -0.247, P = 0.014$),15 implicating anaemia in the increased fatigue perception reported in UC. Vitamin D deficiency is reported at 27% in Crohn's disease and 15% in UC[97] and is associated with adverse effects on disease course.[98] No association was reported between vitamin D deficiency (<50 nmol/L) and fatigue perception in 405 IBD patients.[99] However, vitamin D targets skeletal muscle via genomic100and cell surface vitamin D receptors[101] with roles in calcium metabolism,[102,103] and myocyte proflieration.[88,104,105] In elderly subjects, vitamin D deficiency is associated with reduced muscle function[106]and supplementation improves muscle strength.[107] Consistently, sarcopenia is commoner in paediatric IBD with vitamin D deficiency[108]and cholecalciferol substitution improves muscle power in this cohort.[109] Low serum vitamin D3 (<50 nmol/L) was also independently associated with a greater knee extensor fatigue (361.48, $P = 0.02$) in quiescent adult Crohn's disease2 with vastus lateralis atrophy.[110] In the same subjects, lower Vitamin D3 was found in Crohn's disease with attenuated hypertrophy signalling[110] which may implicate vitamin D deficiency in IBD exercise fatigue. Vitamin B12 has roles in nervous system function,[111] and deficiency is commoner in Crohn's disease than in UC (18.4% vs 5%)[112] most

likely due to the ileal location of Crohn's disease[113] with subsequent resection in a large proportion of cases. Fatigue perception is greater in stroke patients with a lacunar infarct and B12 deficiency relative to those without ($P = 0.01$)[114] suggesting an association between B12 deficiency and fatigue. However, B12 supplementation fails to improve fatigue symptoms in patients with a lacunarinfarct[115] and in both IBD and IBS outpatients[116] suggesting B12 deficiency is not an aetiological factor in quiescent IBD fatigue. Thiamine uptake occurs in the jejunum and is dephosphorylated by thiamine diphosphokinase to produce thiamine pyrophosphate[117]which serves as an enzymatic cofactor of three ketoacid dehydrogenases including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and branched chain α-ketoacid dehydrogenase. Thiamine deficiency is associated with defective skeletal muscle pyruvateoxidation118 and has been linked to IBD fatigue on the basis of defective mitochondrial ATP synthesis.[22,119] High-dosage thiamine improves fatigue perception in quiescent IBD,[22,119] whilst the effect on exercise performance is unknown. The body mass of IBD patients is also known to be increasing,120 and obesity is now a recognised as a metabolic comorbidity in IBD, with prevalence rates between20% and 40%.[121] High visceral fat mass is associated with worsened IBD course[122] and postoperative complciations[123] including diseasereoccurrence.[124] Similarly, metabolic abnormalities associated with obesity such as type II diabetes negatively influence IBD course.[125]Obesity is associated with fatigue in the general population.[126]Peripheral muscle strength,[127,128] anaerobic performance[129] and exercise fatigue resistance[128] are reduced in obese subjects relative to non-obese controls, and the reduction of body mass is associated with improvements in fatigue perception and objectiveperformance.[130] Likewise, concurrent exercise training improves body composition and markers of physical conditioning in obeseIBD.[131]

Fuel and protein metabolism

Hepatic and muscle glycogen stores represent the body store of carbohydrate which is essential for sustained submaximal exercise performance.[132] No data are available on glycogen content in IBD. Both carbohydrate intake[133,134] and whole-body glucose uptake and oxidation during an hyperinsulinaemic-euglycaemic clamp are normal inIBD.[135] However, hyperinsulinemia is reported in active disease andremission[136,137] due to increased β cell function,[137] which despite resulting in elevated HOMA index (i.e., increased insulin resistance),[137]potentially protects against disease relapse.[136] Skeletal muscle insulin sensitivity was consistent to age-matched controls in a small cohort of pedeatric[52] and adult[138] IBD. However, forearm glucose net uptake is blunted in paediatric Crohn's disease in remission relative to active disease.[52] This may suggest greater muscle insulin resistance in quiescent disease and requires further investigation. Available data on energy expenditure in IBD suggest malnutrition is not the result of hypermetabolism. Resting energy expenditure has been shown to be unchanged in IBD[139]; however, other Crohn's disease cohorts demonstrate minor elevations in resting energy expenditure,[140] which is consistent when normalised to fat free mass.[140,141] However, elevated lipid oxidation and reduced carbohydrate oxidation are reported in IBD in the fasted and postprandialstate.[139,140] These metabolic abnormalities have been likened to a starvation phenotype and are further worsened in activedisease.[140] Enteral feeding normalises substrate oxidation in patients[139]and positively influences whole-body protein turnover.[142]Substrate oxidation is further influenced by pharmacological therapy.In paediatric Crohn's disease with active disease, infliximab treatment reduces postprandial carbohydrate oxidation whilst increasing lipid oxidation during parenteral feeding.[143] Whole-bodyprotein turnover is also reduced following initiation of infliximabtherapy[144]; however, concurrent parenteral nutrition infusion reduces proteolysis and increases protein synthesis. This improves protein balance relative to the fasting

state both pre and post infliximab.[144] Infliximab treatment has also increased quadriceps volume (1505 cm3 vs 1569 cm3; $P = 0.010$) and strength (185 Nmvs 214 Nm, $P = 0.002$) in active IBD.[145] Further, corticosteroid treatment increases whole-bodyprotein breakdown in paediatric Crohn's disease[146] and increases postprandial protein oxidation in female Crohn's disease, in addition to increasing carbohydrate oxidation and supressing lipid oxidation in the fasting and postprandialstate.[147] This is consistent with fat deposition and muscle atrophy in Crohn's disease.Sarcopenia is a progressive skeletal muscle disorder characterised by chronic reductions in muscle mass and quality-associated functional deficits.[148] Originally characterised as an age-related problem, sarcopenia is now a recognised comorbidity across chronic disease. The aetiology is complex and includes hormonal factors and attenuated anabolic signalling,[149,150] physical inactivity,[151] motor unit remodelling,[152] muscle deconditioning,[153] increased adiposity[154]and altered muscle phenotype.[155] Sarcopenia prevalence is reported at 42% in IBD156 and is associated with adverse clinical outcomes [157-159] including the need for surgery.[160] Paediatric patients with Crohn's disease of mixed disease activity exhibit anabolic resistance to protein feeding[52] although this did not occur in a small adult cohort with active Crohn's disease.[138] Relative to healthy controls, fatigued Crohn's disease patients with quiescentdisease[2,110] have reduced serum insulin-like growth factor-1(IGF-1)concentrations[2] with muscle biopsies showing an attenuation of anabolic signalling proteins.[110] Thigh muscle cross sectional area was reduced (14%, $P = 0.055$) in these quiescent patients,[110] as also is gastrocnemius cross sectional area in active IBD (3246 • } 417 vs4415 • } 129 μm2, $P = 0.01$).[75] Analysis of myosin heavy chain (MHC)isoforms from gastrocnemius biopsy demonstrates a loss of MHCI and a concomitant upregulation of MHCIIa/MHCII proteins[75]; this was interpreted as evidence of a shift from a slow oxidative, to a fast fatigable phenotype in Crohn's disease. Stratification of fatigued Crohn's disease patients with quiescent disease into high and low phosphorylated: total Akt ratio showed comparable inflammatory markers between groups,

suggesting other factors contribute to attenuated anabolic signalling110 and premature exercise fatigue.[2] Indeed, serum IGF-1,which acts upstream of the mTORC1 hypertrophy signalling pathway,[161] was reduced by 37% in Crohn's disease[2]and was associated with exercise fatigue (serum IGF-1<20 nmol/L,OR 64.72 [1.19, 3529], $P = 0.04$).[2]Objective physical activity measured by accelerometer was consistent between Crohn's disease and controls[2]; however, consistent with disuse atrophy,[151] Crohn's disease with a low phosphorylated:total Akt ratio was less active than the high ratio group ($P = 0.009$).Physical inactivity is reported across the lifespan in IBD,[51,110,162]and despite decreasing surgery rates,[163] inactivity and deconditioning associated with hospitalisation should be considered in fatigue aetiology given the negative effect on skeletal muscle health.[164,165]. Patients with extensive small bowel resection demonstrate greater declines in exercise capacity relative to non-resectedpatients[57] although this may also relate to greater disease burden. Collectively, disease burden,[75] anabolic dysregulation[52,110] reduced protein nutrition,[134] altered substrate metabolism[144,146] and physical inactivity[51,162] poses significant risk for sarcopenia development in IBD and may be additive in effect. The absence of targeted exercise[164] and nutrition intervention capable of restoring inactivity-induced muscle decline,[166,167] suggests that sedentary IBD patients, particularly those hospitalised, are unlikely to recover deficits in muscle quality and may remain functionally compromised into disease remission. This is consistent with muscle atrophy and persistent exercise fatigue in well controlled IBD.[2,110]

The gut microbiome

The gut microbiome is largely composed of Firmicutes andBacteroidetes[168] and plays a r ole i n short chain fatty acid metabolism, prevention of pathogen invasion and epithelial barrierpreservation.[169] Microbial dysbiosis is a recognised factor in IBDpathogenesis[170] and is associated with

fatigue symptoms in chronic disease. Myalgic encephalomyelitis (ME)/chronic fatigue syndrome(CFS) patients have a reduced abundance of *Faecalbacterium,rosburia, Faecalibacterium prausnitzii* and *Alistipes puytredinis cf*relative to controls. Similarly, there is a reduced abundance of*Faecalibacterium* (P = 0.0002, q = 0.006), *Ruminococcus*, (P = 0.0003,q = 0.006), *Alistipes* (P = 0.017, q = 0.16) and butyrate producing taxaincluding *F. prausnitzi* (P = 0.0002, q = 0.007) and *Roseburia hominis*(P = 0.0079, q = 0.105) in quiescent IBD fatigue relative to non-fatiguedpatients.33 Butyrate is a short chain fatty acid synthesised during fermentation of dietary carbohydrate[172] which serves as a fuel source for colonocytes, contributes to barrier integrity[173] and inhibits inflammation.[174] The abundance of butyrate producing taxa is reduced in ME/CFS[175] and in fatigued cancer patients, relative to a low fatigue group.[176] Fatigued IBD patients also showed increased abundance of the pro inflammatory species *Ruminocus gnavus* relativeto non-fatigued patients (P = 0.0019, q = 0.055)[33] which is consistent in ME/CFS.[171] These alterations positively correlate with fatigue perception,[33,171] suggesting probiotic supplementation may improve fatigue burden. This has not been trialled in IBD. Probiotic supplementation has improved anxiety symptoms in CFS[177] but failed to reduce fatigue perception.[178]

CNS changes in IBD

The clinical significance of CNS changes in chronic disease fatigue is poorly understood. A systematic review of 26 structural and functional MRI experiments failed to characterise any consistent correlation with neural fatigue.[179] Grey matter atrophy is reported in IBD patients across a number of brain regions[180-183] which are involved in cognitive, emotional and pain processing.[184] Although neither fatigue facets have been considered as primary outcomes in these experiments, some findings may relate to fatigue aetiology such as grey matter atrophy in the right supplementary motor

area in IBD, concomitant to reduced axonal diffusivity, a surrogate of microstructural integrity, in the right corticospinal tract.[182] These structural alterations may impair central drive and could represent a neural contributor to exercise fatigue in IBD.[2,47] Functional neuroimaging of IBD demonstrates perturbations in emotional processing[184] and stress response.[185] This could be linked to heightened fatigue perception. Grey matter atrophy has been reported in the fusiform gyrus, which is involved in facial recognition[186] and could be linked to the altered stress response shown in IBD via fMRI.[185] Recent brain phenotyping in quiescent Crohn's disease patients with increased fatigue perception show reduced grey matter content in the superior frontal gyrus relative to healthy controls.[183] The superior frontal gyrus is involved in cognitive processing[187] which appears consistent with perturbed emotional processing found inIBD.[184] Moreover, cerebral blood flow was significantly elevated in the grey matter of fatigued Crohn's disease.[183] Inflammation has been implicated in these morphological alterations[181,183]; however, there are no causal data to support this. The hyper perfusion of grey matter in Crohn's disease[183] may be linked to brain inflammation as macrophages are known to secrete nitric oxide188 and are upregulated during inflammatory signalling. Vagal sensory neurons express receptors capable of sampling inflammatory mediators, facilitating gut–brainsignalling.[70] This has been linked to functional,[184,185] metabolic[183]and structural alterations[181] in IBD. Proinflammatory cytokines induce neurotoxic effects.[189,190] Both TNF and IFN-γ cause apoptosis in human oligodendroglial cell lines[191] and IL-1$\alpha$and IL-1βstimulate nitric oxide dependent apoptosis in primary human astrocytes.[192] Inflammation also inhibits neurotransmitter synthesis via oxidation of the enzymatic cofactor tetrahydrobiopterin (BH4),193which is required for serotonin and dopamine synthesis.[194]*Neurotransmitters*The monoamines serotonin, dopamine and noradrenaline are implicated in multiple facets of fatigue aetiology. Serum metabolomics profiling of IBD patients with quiescent disease and heightened fatigue perception showed reduced tryptophan ($\beta = -0.38$,

P = 0.042)relative to non-fatiguedpatients.[33] This requires further investigation as tryptophan is a precursor to serotonin, implicated in fatigueaetiology.[195,196] Serotonin dysregulation is reported in conditions with heightened fatigue perception[197]; however, selective serotonin reuptake inhibitor (SSRI) treatment has failed to target fatigue perception.[198] Similarly, it is hypothesised that increased cerebral tryptophan uptake during prolonged exercise due to tryptophan displacement from albumin[199] and elevated BCAA oxidation[200] increases serotonergic activity, causing fatigue.[196,201,202] However,SSRI treatment demonstrates inconsistent effects on exercise fatigue,[43,203] and the time to exercise exhaustion was consistent between subjects ingesting tryptophan or BCAA[204]; these collective findings dispute the serotonin hypotheses.Dopamine is strongly implicated in the development of fatigue perception and exercise fatigue. MS patients with elevated fatigue perception show reduced glycolytic activity in dopaminergic brain regions relative to non-fatiguedpatients.[205] Consistently, the dopamine reuptake inhibitor methylphenidate improves fatigue perception in CFS,[206] Parkinson's disease[207] and cancer.[208]Methylphenidate also delays exercise fatigue during aerobic cycling at high environmental temperatures.[209,210] In contrast, noradrenaline reuptake inhibition with reboxetine impedes cycling performance[211]and isometric knee extensor exercise[212] by inhibiting cortical voluntary activation.[212,213]

Psychological factors

Psychological disorders are common in IBD,[214] influencing diseasecourse[215,216] and development of fatigue perception.[13] The lifelong medical care required in chronic disease is associated with treatment fatigue, where adherence to treatment regimens reduces due to psychological factors such as pill burden.[217] In quiescent UC, 30% of patients reported pill burden as a reason for non-adherence to medication[218]which likely contributes to

an increased fatigue perception. Psychological factors are known to influence temporal changes in chronic fatigue perception.[77] Similarly, quiescent IBD patients with a self-directedpersonality[60] and a higher sense of coherence[219]report a lower perception of fatigue burden, whilst patients who were able to adapt their behaviour to fit the situation in accordance with their chosen goals, report lower fatigue perception relative to patients who are not able to adapt.[219] Consistently, psychosocial interventions have shown promising results in IBD patients with self-reportedfatigue.[220]In the exercise domain, psychological input such as verbal encouragement[221]and listening to music[222] elicit ergogenic effects. Similarly, psychological deception delays fatigue. Post-exercise handgrip fatigue is significantly attenuated when subjects complete the task whilst observing their non-exercising hand via the use of mirror box.[223] Further, subjects aware of the final stages of exercise can transiently elevate force output.[224] Trained subjects cycling to volitional failure at 80% peak aerobic power (242 ± 24 W) remained able to generate 731 ± 26 W during a sprint performed immediately post task failure.[225] These collective findings suggest psychological state heavily influences both exercise capabilities and chronic fatigue perception.[60,219] Addressing psychological comorbidities in IBD may therefore confer a beneficial effect on overall fatigue burden.

Pain

Abdominal pain in IBD is reported in in 50%-70%of active IBD patients[226]and attributed to sensory afferent signalling within the gastrointestinal tract to the CNS[227,228] due to factors such as inflammation, strictures, small-bowel obstruction and dysmotility.[229]However afferent signalling also relays joint inflammation into theCNS[230] and 16% of IBD patients report non inflammatory jointpain.[231] As with fatigue perception, pain often persists during remission and prevalence is reported at 20%.[226]Similarities in brain morphology between IBD and chronic pain conditions have

been noted[184]; however, the relationship between pain and fatigue perception is poorly characterised. Rheumatoid arthritis patients demonstrated synchronous fluctuations in pain and fatigue perception during a 1-yearmeasurement period,[232] suggesting co-presentation of these symptoms rather than one preceding the other in a temporal fashion. However, objective data suggest the symptoms have distinct mechanisms, as changes in pain and fatigue perception following treatment with TNF inhibitors relate to differential morphological alterations.[233]

Treatment-related factors

Fatigue is a reported side effect of many medications used in IBD.Treatment with immunomodulators such as azathioprine is associated with increased fatigue perception in Crohn's disease patients.[13]The initiation of thiopurine therapy caused marked fatigue, which rapidly resolved following cessation of treatment.[234]Anti-TNFtreatment at baseline was linked to more severe fatigueperception,[235] and the cessation of biological therapies was associated with reduced fatigue perception.[13]In contrast, 12 weeks of conventional therapy consisting of5-aminosalicylates,corticosteroids and/or thiopurine reduced fatigue perception in a cohort of 82 newly diagnosed UC patients,[236] whilst infliximab[14] and adalimumab[21] treatments have also reduced fatigue perception. The contrasting data linking such therapies to increased fatigue perception[13,235] suggest disease activity is a confounding factor rather than any specific drug-related effect. Glucocorticoid treatment is associated with higher fatigue perception in IBD13 which may relate to the potent catabolic effects of glucocorticoids on skeletal muscle.[146,147] Glucocorticoids induce the E3 ubiquitin ligase muscle RING finger protein 1 (MuRF1) dependent degradation of skeletal muscle contractile proteins[237] and inhibit muscle metabolic[238] and contractile function.[239] In female IBD patients, body cell mass was negatively correlated with cumulative prednisolone dose (φ =

−0.318, $P = 0.011$).[50] This may relate to premature exercise fatigue in female IBD.[47,49,53] Although leg endurance positively correlated with corticosteroid dosage ($r2 = 0.50, P < 0.001$)[47] in a mixed gender Crohn's disease cohort. Limitations in the experimental design of existing data prevent more resolute conclusions on drug factors relating to IBD fatigue.

Management Strategies

Pharmacological management

An open label pilot study demonstrated complete regression of fatigue at 20-dayfollow-upin 10 out of 12 patients prescribed high dosages of thiamine[119] (Table 1). Fatigue was assessed pre and post-intervention by the CFS scale. Despite a limited sample size and lack of appropriate statistical analyses, these findings have been corroborated in a recent RCT, where high-dose thiamine administration in IBD patients significantly reduced fatigue perception relative toplacebo.[22]Existing data on the efficacy of anti-TNF therapy on fatigue in IBD are inconclusive. Fatigue perception assessed as a secondary outcome using the multiple fatigue inventory 20 scale (MFI-20)following4 weeks of infliximab therapy was significantly reduced relative to a placebo infusion until the end of the study period. The placebo infusion rapidly decreased fatigue scores, before returning to baseline within 14 days, suggesting a substantial placebo effect.[14] Consistently, fatigue perception assessed as a secondary outcome measure using the FACIT-F scale significantly decreased following adalimumab therapy (40 mg every 2 weeks) in a cohort of 499moderate-to-severe Crohn's disease patients.[21] It was beyond the scope of these experiments to extrapolate the mechanisms facilitating improvements in fatigue

perception. It is likely the positive effects observed were the by-product of reduced disease activity, given the association between disease activity and fatigue.[76,78] Interestingly, infliximab treatment increased knee extensor volume and isokinetic strength in adult Crohn's disease[145] suggesting infliximab may also positively influence exercise fatigue. However, 28% of 198 fatigued IBD patients remained fatigued following 54 weeks of biological therapy, despite achieving clinical remission (HBI ≤4 or SCCAI ≤2 and CRP <8 mg/L).[78] This demonstrates the failure of biological therapy to reduce fatigue perception in a large proportion of patients. Currently available data do not support the use of anti-TNFtreatment for the sole treatment of IBD fatigue, and further work is required to characterise the effects on fatigue perception and exercise deficits in IBD.

Psychosocial management

Psychosocial interventions have been trialled in IBD given the prevalence of psychological comorbidity. Both therapist-led and self-directed stress management programmes reduced self-reported tiredness, assessed as a secondary outcome at 6-and12-monthfollow-upin Crohn's disease patient using a Crohn's disease symptom diary on a 1-3scale in ascending severity (Table 2).[240] Problem solving therapy (PST) and solution-focused therapy(SFT) reduced self-reported fatigue perception by 60% and85.7% respectively in quiescent Crohn's disease patients during a 12-weekpilot intervention.[20] Encouraged by these findings, the same group performed a 12-weekrandomised controlled trial comparing SFT to care as usual in a sample of 98 fatigued Crohn's disease patients in remission.[220] SFT reduced fatigue perception relative to care as usual ($P < 0.001$). This remained consistent at 6-monthfollow-up ($P < 0.010$) but not a t 9 months ($P = 0.610$).These positive effects were attributed to cognitive reappraisal and reduced self-perception of illness in the patients. The diminished effect observed at 9 months was attributed to absence of follow-up plans.

However, these interventions only target psychological facets of fatigue aetiology, leaving many other contributing factors unaddressed. This may account for the transient effect on self-reported fatigue perception.

Physical activity interventions

Exercise training interventions in chronic diseases presenting with muscle wasting, deconditioning and fatigue such as cancer and MS, have a positive effect on fatigue perception and physical function.[241,242] Fatigue has not been considered as a primary outcome measure in response to exercise training in IBD.Mcnelly and colleagues compared the effect of increased physical activity and/or omega-3fatty acid supplementation on fatigue in a cohort of 52 IBD patients in remission (CRP <5 mg/ld. adobe <5). Fatigue assessed using the FACIT-increased with omega-3supplementation, with no effect of the exercise intervention when compared to placebo. Conversely, fatigue quantified via the IBD fatigue questionnaire (IBD-Scale) showed a reduction in fatigue in the exercise advice group compared to placebo, with no effect observed for omega-3supplementation[243] (Table 3). The divergent findings between scales make it difficult to draw any firm conclusions pertaining to these subjective outcomes. A recent six month resistance training intervention in 23 IBD patients reduced fatigue perception, quantified by the IBD fatigue scale(IBDF) ($P < 0.005$) as a secondary outcome, in addition to increasing lumbar spine bone mineral density (BMD) ($P < 0.001$) and isometric elbow and knee extensor strength ($P < 0.001$) relative to a controlgroup.244 Peripheral muscle function[2,31,47,50] and cardiorespiratoryfitness[31,55,57] a reduced i n I BD and to a greater extent in those with fatigue complaints.[31] We postulate that this multi organ disruption is likely a significant contributor to fatigue aetiology. The restoration of metabolic and physiological function by exercise training reduces fatigue burden in other

chronic disease with high prevalence of sarcopenia and fatigue.[241,242,245,246] This suggests exercise training intervention may represent a pragmatic strategy to improve IBD fatigue. However, fatigue and deconditioning have not been considered as primary outcome variables in IBD exercise studies. Both low-[247]and high-intensity[248]aerobic exercise training interventions improve VO2 peak in IBD patients (Table 4).Secondary to increasing quality of life and reducing self-reportedstress.[247,249] Resistance exercise training increases BMD[244,250] and muscle strength[53,244,251] i n I BD (Table 5). Concurrent resistance and aerobic exercise training in obese IBD patients reduced body fat percentage and increased lean body mass and estimated VO2peak[131] but had no effect on the gut microbiota. However, the gutmicrobiota of obese subjects is known to respond differentially to exercise training relative to lean subjects.[252,253] Orocecal transittime and intestinal permeability is consistent in Crohn's disease relative to healthy controls following moderate intensity cycling,[259]whilst immune cell and cytokine responses to moderate and high-intensity cycling are consistent between paediatric Crohn's and healthy children.[254] Available data support the implementation of exercise training as an adjunctive therapy as IBD patients can safely participate in multiple training modalities[131,254] and demonstrate positive functional and psychological outcomes.[247,249]Exercise has a positive effect on IBD disease course,[255] and marked favourable outcomes are associated with increased muscle masspre-hospitaladmission.[256] Exercise increases the abundance of butyrate producing taxa and faecal acetate and butyrate concentrations in healthy subjects,[252] and athletes show altered gut microbial pathways for amino acid and carbohydrate metabolism and greater faecal short chain fatty acid concentrations.[257] This is of interest in IBD as dysregulated amino acid metabolism and reduced butyrate producing taxa are reported in fatigued IBD patients with quiescent disease relative to non-fatiguedpatients.[33]

Conclusion

IBD fatigue is a multifaceted symptom likely requiring multi-modal treatment strategies (Figure 2). We speculate that the fundamental aetiological factors include inflammation, physical deconditioning, altered brain morphology,[183] nutritional factors,[50] psychosocial disturbance[77]and sleep difficulties.[59] The relative contribution of these factors relates to disease activity. In the initial treatment of IBD fatigue, potentially reversible factors like active disease, anaemia and micronutrient deficiencies including iron, vitamin B12, thiamine[22] and vitaminD[109] should be targeted. When fatigue burden persists, adjunctive therapies such as psychosocial intervention[220] should be considered to address psychological contributions to fatigue. Likewise, exercise training intervention improves fatigue burden in other chronic disease with muscle decline[241,242] and represents a pragmatic management strategy for IBD fatigue that could be trialled immediately.

viii. References

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ix. Tables

Table 1. Pharmacological interventions where fatigue perception has been assessed as either a primary or secondary outcome variable.

Author	Intervention	Control	Participants	Outcomes	Results
Costantini *et al* (2013)[119]	Oral Thiamine administration at 600mg / day. Additional 300mg/day up to 1500mg /day dependent upon fatigue response	NA	8 UC & 4 Crohn's disease in remission.	• Fatigue perception (CFS) • Thiamine and thiamine pyrophosphate concentrations	• Ten patients (4 Crohn's disease) showed complete regression of fatigue (CFS scores 0). • 2 UC patients showed moderate-low fatigue (≤13 CFS) • Thiamine and thiamine pyrophosphate concentrations increased in all patients.
Minderhoud *et al* (2007)[14]	Placebo administered at baseline followed by Infliximab treatment (5mg/kg) at 2 weeks post.	NA	14 active Crohn's disease	• Fatigue (MFI-20) • Depression (CES-D)	• Infliximab reduced fatigue measured at weekly intervals from weeks 1-4 ($P < 0.05$)

	Additional dose at 4 weeks post for patients with fistulae.			• Quality of life (IBDQ)	• Placebo reduced fatigue at 3 and 7 days post infusion (P<0.01) only. • QOL increased (P < 0.005). • Depression reduced (P < 0.01).
Loftus *et al* (2008)[21]	Phase III randomized double blind clinical trial (CHARM) evaluating HRQOL outcomes between adalimumab maintenance and induction only treatment. Adalimumab maintenance therapy (40 mg every other week).	Adalimumab induction-only, followed by placebo	499 randomised responders (reduction of ≥70 points from baseline CDAI)	• Depression (Zung self-rating depression scale) • FACIT-F • Pain • IBDQ • SF-36	• Adalimunab maintenance therapy: • Reduced depression (P <0.01), fatigue (P < 0.001) and abdominal pain (P < 0.05) • Improved QOL (P < 0.05) and medical outcomes (P < 0.05)
Bager *et al* 2020[22]	RCT of high-dosage oral thiamine (600-1800mg/day)	Randomised double-blind, placebo controlled crossover design	40 quiescent, fatigued IBD patients	• Fatigue (IBDF-scale)	• Thiamine treatment reduced fatigue by 4.5 points, 95% CI 2.6-6.2 vs 0.75 points 95% CI -1.3-2.9 in placebo (P = 0.0003).

Abbreviations: Health related quality of life (HRQOL), Chronic Fatigue Syndrome scale (CFS), Multiple-Fatigue Inventory 20 – (MFI-20),), Centre for epidemiological studies depression scale (CES-D, IBD Quality of life questionnaire (IBDQ, Functional assessment of chronic illness therapy (FACIT)-Fatigue, Medical Outcomes Study 36-tem Short form health survey (SF-36, Functional assessment of chronic illness therapy (FACIT)-Fatigue.

Table 2.Psychosocial interventions where fatigue perception has been assessed as either a primary or secondary outcome variable.

Author	Intervention	Control	Participants	Outcomes	Results
Garcia-Vega *et al (2004)*[240]	Stress management techniques (group taught vs self-directed learning)	Standard of care	45 Crohn's disease patients in remission.	Symptom Diary: • General discomfort • Tiredness • Diarrhoea • Constipation • Abdominal pain • Distended abdomen	• Stress management training improved: Tiredness (P<0.01), constipation (P<0.1), abdominal pain (P<0.5) and distended abdomen (P<0.5). • Self-directed stress management improved tiredness (P<0.1) and abdominal pain (P<0.5) • No effect of standard of care / control group.
Vogelaar *et al* (2011)[20]	Pilot study on SFT vs PST as a fatigue treatment in IBD.	Standard of care / Care as usual	29 Crohn's disease patients in remission	• Fatigue (CIS) • Quality of life (IBDQ)	• Fatigue reduced by 85.7% following 12-weeks of SFT • Fatigued reduced by 60% following PST • Fatigue reduced by 45.5% in the treatment as usual control group

					• Non-significant increases in QOL in both interventions.
Vogelaar *et al* (2013)[220]	Randomised controlled trial on solution focused therapy to improve fatigue and quality of life in IBD	Randomised to SFT or care as usual control group.	98 patients IBD patients in remission	• Fatigue (CIS) • Quality of life (IBDQ) • Health Status (SF-36)	• SFT reduced fatigue perception at 3 ($P < 0.001$) and 6 months follow up ($P = 0.010$) but not at 9 months ($P = 0.610$) • QOL improved in the SFT group relative to CAU at 3 months post ($P = 0.02$) • SF-36 physical improved at 3 months post ($P = 0.07$) • The improvements in QOL and SF-36 did non-significant at 6 and 9 months follow up.
Artom *et al* (2019)[258]	Feasibility randomised controlled trial. CBT group received a fatigued based CBT manual, one 60-min and seven 30-min telephone sessions with a therapist over 8-weeks.	Control group received a fatigue information sheet without therapist support.	31 IBD patients in remission. 15 randomised to CBT.	• Fatigue (IBDF scale) • Quality of life (IBDQ)	• Relative to control intervention, CBT intervention improved fatigue perception across both subsections of the IBDF scale section 1, 0.84 (-0.5, 1.82) and section 2, 1.2 (-0.13, 2.27) • QOL was also improved in the CBT intervention relative to the control -0.25 (- 1.21, 0.72).

Abbreviations: Solution focused therapy (SFT), Problem solving therapy (PST), Checklist Individual Strength (CIS), IBD Quality of life questionnaire (IBDQ), Quality of life (QOL), Study 36-tem Short form health survey (SF-36), IBD Fatigue scale (IBDF).

Table 3. Physical interventions where fatigue perception has been assessed as either a primary or secondary outcome variable.

Author	Intervention	Control	Participants	Outcomes	Results
Mcnelly *et al* (2016)[243]	Pilot randomised controlled trial (2x2 factorial design).	Group 1: Exercise advice and omega3 Group 2: Exercise advice and placebo Group 3: No exercise and omega-3 Group 4: No exercise and placebo.	52 Crohn's disease patients in remission	• Fatigue (FACIT-f, IBF Scale)	Fatigue assessed using the FACIT-f: • Exercise advice had no effect on fatigue perception compared to placebo (*P* = 0.38) • Omega-3 supplementation worsened fatigue perception (*P* = 0.02) Fatigue assessed via IBDF Scale Section 1: • Exercise advice intervention reduced fatigue (*P* = 0.03) • Omega-3 supplementation had no effect on fatigue (*P* = 0.42)

Abbreviations: Functional assessment of chronic illness therapy (FACIT)-Fatigue, IBD Fatigue Scale (IBDF).

Table 4. Physiological responses to IBD aerobic exercise training intervention.

Author	Intervention	Participants	Outcomes	Results
D'Inca *et al* 1999[259]	60-minute cycling at 60% VO_2 peak.	6 quiescent ileal Crohn's disease 6 healthy age-matched controls	• Orocaecal transit time • Intestinal permeability • Polymorphonuclear leucocyte function • Lipoperoxidation • Antioxidant status	• Exercise increased orocaecal transit time similarly in Crohn's disease (72 ± 30 vs 100 ± 34 minutes) and HV (77 ± 20 vs 83 ± 23). • Neutrophil chemiluminescence increased post-exercise similarly in both CD and HV. • Urinary zinc output increased in CD. • No change in intestinal permeability or lipoperoxidation in CD or HV.
Loudon *et al* 1999[247]	Thrice weekly walking for 12 weeks	12 sedentary Crohn's disease with inactive or mildly active disease	• Disease activity (HBI) • QOL (IBD Q) • Stress (IBD stress) index • VO_2 Peak	Intervention improved: • Disease activity (HBI) (P = 0.02) • Quality of life (IBDQ) (P = 0.01) • Stress perception (IBD Stress index) (P = 0.0005) • VO_2 peak (P = 0.0013) Trend toward BMI reduction (P = 0.068)
Ng *et al* 2007[249]	Thrice weekly walking for 12 weeks	32 Crohn's disease with	• QOL (IBDQ) • IBD Stress index	Intervention improved: • Disease activity (P<0.05) • Quality of life (P<0.05)

		mildly active or quiescent disease.	• Disease activity (HBI)	• Stress (P<0.05)
Ploeger *et al* 2012[254]	Acute bout of MICT (30 minutes at 50% PMP) and HIIT (6 x 4x15s at 100% PMP.	15 Paediatric Crohn's disease in remission 15 healthy aged-matched controls.	Plasma concentrations of: • Immune cells • Growth factors • Pro-inflammatory cytokines	Relative to high intensity cycling, moderate intensity cycling increased leukocytes,neutrophils,lymphocytes,monocytes,IL-6 and GH increased in Crohn's disease (P < 0.05). • IGF-1 decreased during moderate intensity cycling in Crohn's disease (P < 0.05). • Monocytes remained elevated post exercise and during recovery from MICT in Crohn's disease (P < 0.05). • TNF responses to HIT and MICT were consistent between Crohn's disease and controls. • IL-6 was increased post exercise and in the recovery period in Crohn's disease and controls (P < 0.05) • IL-6 remained elevated post recovery in controls only (P<0.05) • All other responses in Crohn's disease were consistent to healthy controls.
Tew *et al* 2019[248]	Pilot RCT comparing MICT:30 minutes at 35% watt peak and HIT: 10 x 60s at 90% watt peak.	13 HIIT 12 MICT 11 usual care control. Remission or mildly active disease.	• VO_2 peak mL/min/kg • Compliance • Feasibility	• HIIT increased VO_2 peak relative to MICT (2.4 vs 0.7mL/kg/min). • Attendance was 62% for HIIT and 75% for MICT. • Positive feedback on the interventions from patients • 3 non-serious adverse events. Two patients experienced disease relapses during follow up.

Abbreviations: Quality of life (QOL), IBD Quality of life questionnaire (IBDQ), Harvey Bradshaw Index (HBI), Growth hormone (GH), Insulin-like growth factor -1 (IGF-1), Interleukin-6 (IL-6), Peak mechanical power (PMP)Moderate intensity continuous training (MICT), High intensity interval training (HIIT),

Table 5. Physiological responses to IBD resistance exercise training intervention.

Author	Intervention	Participants	Outcomes	Results
Robinson *et al* 1998[250]	One year home-based RET	Quiescent IBD Control group (57) Exercise group (60)	• BMD	BMD increased at the: • Femoral neck, Lumbar spine, Trochanter, Wards triangle ($P > 0.05$) In fully compliant patients, BMD increased at the: • Femoral neck, lumbar spine, wards triangle ($P > 0.05$) • Trochanter 7.77 ± 8.2% vs 3.1 ± 5.83% ($P = 0.02$)
Candow *et al* 2002[251]	Twelve week RET	12 Crohn's disease in remission. No control group.	• HBI • 1RM Leg press • 1RM Chest press	• No change in disease activity pre – post (HBI 4.1 vs 3.9 ($P > 0.05$) • Leg press increased 26%, chest press increased 21% ($P < 0.05$).
De Souza Tajiri *et al* 2014[53]	Eight week, knee extensor RET	10 Crohn's disease & 9 UC outpatients with pre-defined quadriceps weakness.	• Thigh circumference • Knee extensor 1RM • Isometric knee extensor strength • IBDQ	• Body mass ($P = 0.73$) and thigh circumference ($P = 0.32$) did not change following RET. • Maximal isometric thigh strength increased ($P = 0.0001$) • 1RM leg extension increased ($P = 0.0001$) • All components of the IBDQ scale increased ($P = 0.0001$)

Cronin *et al* 2019 [131]	Eight week concurrent training intervention	13 Exercise group and 7 controls. All obese IBD in clinical remission.	• Body composition (DEXA) • Cardiorespiratory fitness (estimated VO_2 max)	Concurrent exercise training: • Increased median estimated VO_2 max (43.41 ml/kg/min vs 46.01 ml/kg/min; (P = 0.03). • Reduced median body fat 2.1% (P = 0.022). • Increased median lean mass 1.59kg (P = 0.003) • Decreased median fat mass 1.52kg (P = 0.487)
Jones *et al* 2020[244]	Six months RET	47 Crohn's disease (23 exercise, 24 control)	• BMD • Muscle Function (isokinetic strength, chair stand test and arm curl test) • Fatigue (IBDF scale)	Relative to a control intervention, exercise increased: • Lumbar spine BMD (P <0.001) and femoral neck BMD (P=0.059). • Grip strength (P < 0.001), upper and lower limb isokinetic strength (P < 0.001) and function (P < 0.001). Exercise decreased fatigue perception (IBDF scale) (P = 0.005).

Abbreviations: Dual energy X-ray absorptiometry (DEXA), Bone mineral density (BMD), One repetition maximum (1RM), Harvey Bradshaw Index (HBI), IBD Quality of life questionnaire (IBDQ), IBD Fatigue scale (IBDF), Resistance exercise training (RET).

x. Figure Legends

Figure 1Theoretical schematic of IBD fatigue aetiology. Light blue boxes relate to active disease mechanisms, Light green boxes relate to available data in quiescent disease and yellow boxes are factors which can occur regardless of disease activity. Green outline represents upregulated processes whilst red outlines represent downregulated processes.). Closed arrows represent aetiological factors predominantly contributing to one fatigue domain. Open arrows represent aetiological factors that can contribute to either fatigue domain. Whilst some mechanisms predominate in either fatigue domain, there is an inherent overlap between domains (i.e, reduced physical activity and associated deconditioning will impact both exercise fatigue and fatigue perception).

Figure 2. Simplified overview of aetiological factors in IBD fatigue and potential treatment strategies to target the specific factors.

1. Authors declaration of personal interest:

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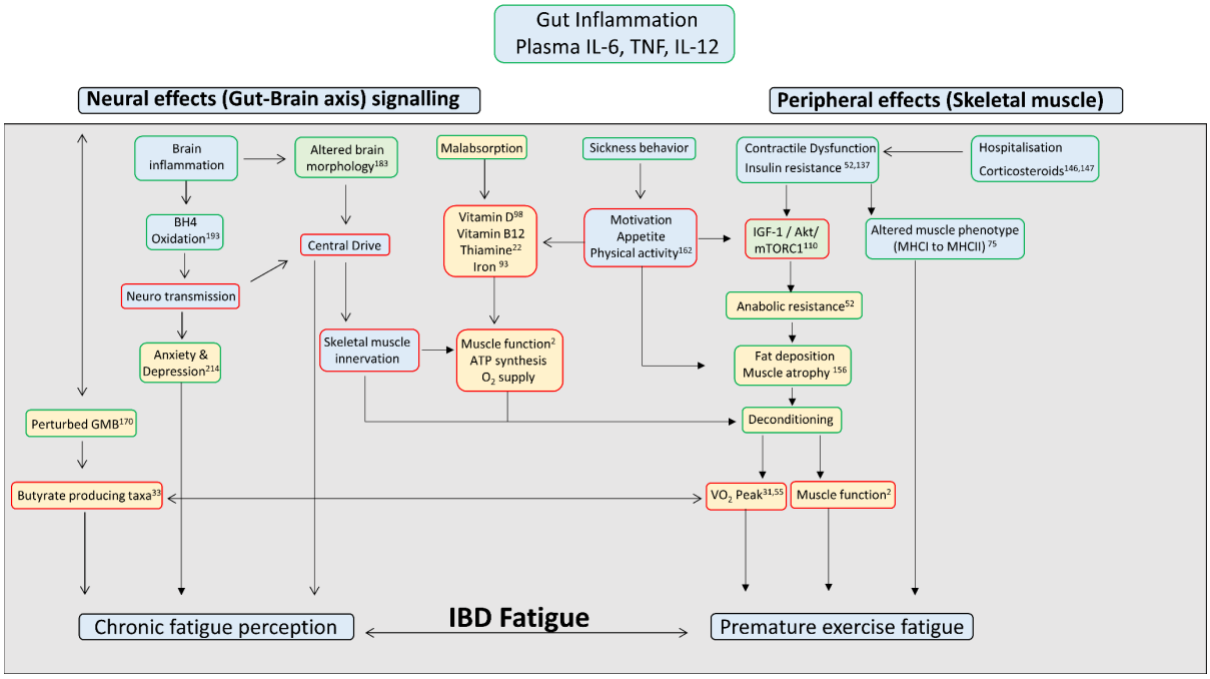
Gut Inflammation
Plasma IL-6, TNF, IL-12
Neural effects (Gut-Brain axis) signalling
Peripheral effects (Skeletal muscle)
Brain inflammation
Altered brain morphology[183]
Malabsorption
Sickness behavior
Contractile Dysfunction
Insulin resistance [52,137]
Hospitalisation
Corticosteroids[146,147]
BH4 Oxidation[193]
Central Drive
Vitamin D[98]
Vitamin B12
Thiamine[22]
Iron [93]
Motivation
Appetite
Physical activity[162]
IGF-1 / Akt/ mTORC1[110]
Altered muscle phenotype (MHCI to MHCII) [75]
Neuro transmission
Anabolic resistance[52]
Anxiety & Depression[214]
Skeletal muscle innervation
Muscle function[2]
ATP synthesis
O_2 supply
Fat deposition
Muscle atrophy [156]
Perturbed GMB[170]
Deconditioning
Butyrate producing taxa[33]
VO_2 Peak[31,55]
Muscle function[2]
Chronic fatigue perception
IBD Fatigue
Premature exercise fatigue

Figure 1.

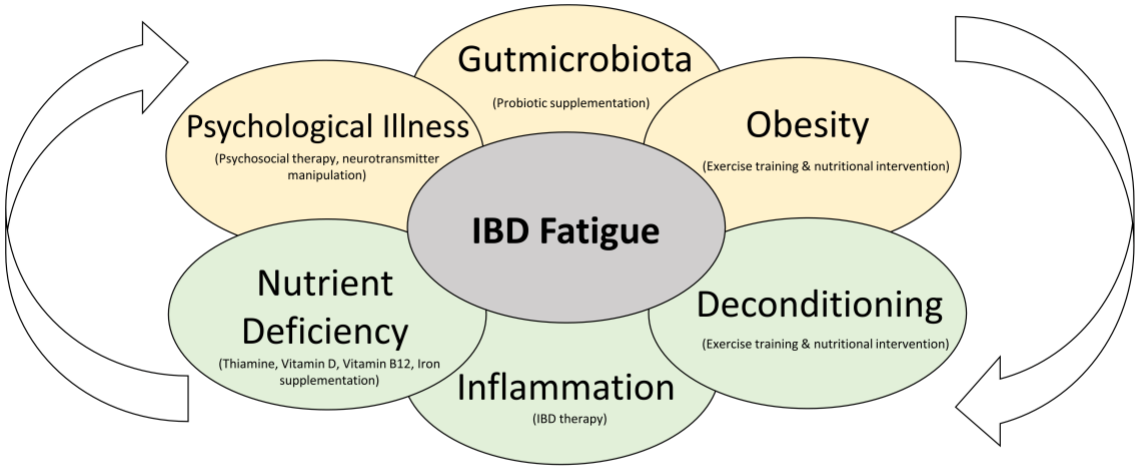
Gutmicrobiota
(Probiotic supplementation)
Psychological Illness
(Psychosocial therapy, neurotransmitter manipulation)
Obesity
(Exercise training & nutritional intervention)
IBD Fatigue
Nutrient Deficiency
(Thiamine, Vitamin D, Vitamin B12, Iron supplementation)
Deconditioning
(Exercise training & nutritional intervention)
Inflammation
(IBD therapy)

Figure 2